REMARKS

Claims 1-29 are pending in this application. Claims 10-29 have been withdrawn as being directed to a non-elected invention.

Claim 4 has been amended to correct typographical errors contained therein. Claim 6 has been amended for clarification purposes. The amendments do not add new subject matter within the meaning of 35 U.S.C. §132. Therefore, entry of the amendments is respectfully requested.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, the Examiner objects to Claims 4-6

The Examiner requests correction of the term "solubule" in claim 4. Accordingly, Applicant's have amended claim 4 to correct this typographical error.

In view of the foregoing, the Examiner is respectfully requested to withdraw this objection.

II. At pages 3-4 of the Official Action, claims 1-9 have been rejected under 35 USC § 112, second paragraph, as being indefinite.

The Examiner asserts that the metes and bounds of the phrase "recombinant amoidogenic proteins form a mixture" in claim 1 are unclear. Specifically, the Examiner states that it is unclear "whether the recombinant amyloidogenic proteins refer to multiple molecules of the same protein or actually different recombinant proteins, i.e., proteins with different sequences and/or structures.

Applicants respectfully traverse this rejection.

MPEP §2171 states that the requirement of 35 U.S.C. §112, second paragraph is "whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art."

The phrase "amyloidogenic proteins" is intended to refer to any type of amyloidogenic proteins of homogenous or heterogeneous chemical composition. The limitation recited in claim 1 is recombinant amyloidogenic proteins. As such, the scope of the claim would be clear to a hypothetical person possessing the ordinary skill in the pertinent art, and claim 1 particularly points out and distinctly claims the invention.

Therefore, the Examiner is respectfully requested to withdraw this rejection of claim 1.

The Examiner further asserts the limitation "significantly below critical micelle concentration" in claim 3 is unclear because it is unclear as to what would suffice as being significantly below critical micelle level.

Applicants respectfully traverse this rejection.

Applicants submit that the plain and ordinary dictionary definition makes it clear that the phrase indicates a dilution of the solution of step a) of claim 3 which prevents micelle formation of the lipids used. However, solely for the sake of furtherance of prosecution and without prejudice or disclaimer, Applicants have amended claim 3 to clarify that the "dilution of the solution of the water soluble complexes of lamellar lipid structures and oligomeric intermediate structures below critical micelle concentration." As such, the scope of the claim would be clear to a hypothetical person possessing the ordinary skill in the pertinent art, and claim 3 particularly points out and distinctly claims the invention.

Therefore, the Examiner is respectfully requested to withdraw this rejection of claim 3.

Additionally, with respect to claim 3, The Examiner also asserts the limitation "and treatment of the so produced amyloidogenic aggregates with non-denatured detergents" is unclear. Specifically, the Examiner states that one of skill in the art would not know if the aggregates in step b) are produced as a result of dilution of the solution of water soluble complexes or as a result of dilution and addition of non-denaturing detergents. The Examiner asserts that preamble implies that the result of each step in claim 3 may result in the production of amyloidogenic aggregates and it is unclear when the resulting aggregates are produced in step b) of the instant claim.

Applicants respectfully traverse this rejection.

Applicants submit that steps a) and b) are recited in the alternative. Therefore, the phrase in question, when read in context of step a) or step b), clearly is an additional process of step b). Thus, amyloidogenic aggregates according to this claim are produced by the process of step a) or alternatively by step b), which contains an additional step. Hence, the skilled artisan upon

reading the claim would understand that either step a) or step b) produce the claimed aggregates. As such, the scope of the claim would be clear to a hypothetical person possessing the ordinary skill in the pertinent art, and claim 3 particularly points out and distinctly claims the invention.

Therefore, the Examiner is respectfully requested to withdraw this rejection of claim 3.

The Examiner asserts the limitation "amyloidogenic oligomeric ß-sheet intermediate structure is an oligomeric ß-sheet intermediate ($PrP^{ß}$)" in claim 4 is unclear since one of skill in the art would not understand how a ß-sheet structure is an intermediate protein.

Applicants respectfully traverse this rejection.

Applicants submit that the skilled person in the art in the instant case is proficient in the technical area of amyloidogenic proteins, particularly prion proteins. It is known in the art that prion proteins, upon forming the ß-sheet structure in nature, typically become insoluble and precipitate immediately. The instant subject matter provides for soluble amyloidogenic ß-sheet intermediate structures that have a ß-sheet structure and form aggregates but do not precipitate until further treated. Therefore, they are ß-sheet containing and intermediate in that the final precipitating ß-sheet structure is not yet reached. As such, the scope of the claim would be clear to a hypothetical person possessing the ordinary skill in the pertinent art, and claim 4 particularly points out and distinctly claims the invention.

Therefore, the Examiner is respectfully requested to withdraw this rejection of claim 4.

Applicants submit that the skilled person in the art is proficient in the technical area of amyloidogenic proteins, particularly prion proteins. It is known in the art that prion proteins upon forming the ß-sheet structure in nature they typically become insoluble and precipitate immediately. Because the instant subject matter provides for soluble amyloidogenic ß-sheet intermediate structures that have a ß-sheet structure and form aggregates but do not

precipitate until further treated. Therefore, they are ß-sheet containing and intermediate in that the final precipitating ß-sheet structure is not yet reached. As such, the scope of the claim would be clear to a hypothetical person possessing the ordinary skill in the pertinent art.

Therefore, the Examiner is respectfully requested to withdraw this rejection of claim 4.

The Examiner asserts the limitation "the pH of the conversion buffer is below the isoelectric point of the recombinant amyloidogenic proteins" of claim 9 is unclear. Specifically, the Examiner states that if there are plural types of amyloidogenic proteins in the solution, each assumingly would have their own isoelectric point. For this reason, the Examiner contends that one of skill in the art would not know what pH would suffice to be below "the isoelectric point" as recited in the claim.

Applicants respectfully traverse this rejection.

Applicants submit that the skilled person in the art has read the general description of the invention, as well as the profuse prior art teaching that there are more than one amyloidogenic proteins found in nature. Thus, one of skill in the art would understand that the isoelectric point is related directly to the particular protein being used in accordance with the claimed methods. Specifically, one of skill in the art, when faced with two possible proteins, would immediately either choose a pH for the conversion buffer that suits all isoelectric points of the different proteins present or select a pH below the isoelcectric point of the recombinant amyloidogeonic proteins most important to him/her. Accordingly, the choice of pH of the conversion buffer does not go beyond routine knowledge of one with skill in the art.

Therefore, the Examiner is respectfully requested to withdraw this rejection of claim 9.

III. At page 5 of the Official Action, claim 1 has been rejected under 35 USC § 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al.

The Examiner asserts that it would have been obvious to the skilled artisan to modify the method of observing increased beta-sheet formation with the insertion of protein into a lipid bilayer of Kleinschmidt with use of amyloid proteins by Pan et al. because Pan shows attempts of producing beta-sheet containing soluble amyloid proteins.

Applicants traverse this rejection.

Kleinschmidt et al. teaches that unfolded outer membrane protein A (OmpA) of *Escherichia coli*-specific protein contains 5 tryptophan residues and inserts into lipid bilayers via three structurally distinct membrane-bound folding intermediates and features four ß-hairpins. See, Abstract. In other words, OmpA is a highly specific protein artificially forced to unfold by denaturing urea and inserts into lipid layers in order to regain its original natural structure in the absence of urea.

Pan et al. teaches the conversion of α-helices into ß-sheets of amyloid proteins. As stated above, the Examiner alleges Pan shows attempts of producing ß-sheets containing soluble protein. However, the vague teaching cited, i.e., pages 10965-10966, shows no such attempt, and instead there is only a comprehensive discussion of α-helix/ ß-sheets conversion leading to precipitation.

Accordingly, the basis of the Examiner's rejection is missing, and the references do not show what has been alleged in support thereof. Furthermore, the teaching of Kleinschmidt relates to a very specific protein in specific prokaryotes and this specific protein lacks any relevant similarities to the instantly claimed subject matter. Furthermore, the cited references do not teach identities in sequence and protein structure with mammalian amyloidogenic proteins. Further still, the teachings of Kleinschmidt are not related directly to ß-sheet but specifically to four ß-hairpins, and there is also no increase in ß-sheet but merely a refolding into ß-hairpin structures.

It is common knowledge in the art, that proteins differing in sequence and structure are highly unlikely to have common folding properties. To the contrary, in most proteins even subtle differences in sequence are known to have strong implications on the resulting secondary and tertiary structure. Due to this knowledge in the art, there would be no reason or suggestion to transfer the specific teaching of a particular prokaryotic protein relating to its urea/lipid bilayer-induced refolding capability based on a specific tryptophan-based ß-hairpin structure to another specific eukaryotic protein with a totally different sequence, secondary and tertiary structure. The skilled person would not have considered Kleinschmidt to provide a teaching useful for increasing the content of ß-sheet secondary structure in mammalian amyloid proteins in general, because OmpA does not increase ß-sheet content. To the contrary, the method of the instant claims increases the ß-sheet content to the extent that the resulting aggregates remain soluble.

Additionally, the water soluble complexes formed according to claim 1 have lamellar lipid structures. Lamellar lipid structures differ from the typical spherical micelles, because they have a flattened lamellar structure, i.e., a disc-shaped flat structure with the negative charges pointing to the outside and the hydrophobic portions accumulated on the inside. Due to this disc shaped structure the inner environment is very dense and completely hydrophobic. The lamellar lipid structures are essential for arriving at the soluble amyloidogenic oligomeric ß-sheet intermediate structures. Typically, they are produced by mixtures of lipids, such as, by way of nonlimiting example, DMPC, DMPS, and DHPC, (See, publication of instant application no. 20040143093 at paragraph 34) with one type being shorter and forming U-turn and the other longer type forming the side walls aligned opposite to each other. None of the prior art cited teach, or let alone provide any reason or suggestion to modify their respective teachings, alone or together, the use of such specific lipid structures for increasing the ß-sheet content of amyloidogenic proteins.

In view of the remarks set forth herein, it is submitted that nothing in the cited references, whether taken alone or in combination, render the subject matter of claim 1 obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. At pages 6-11 claims 2-9 have been rejected under 35 USC § 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al., as applied to claim 1, and in further view of the references, as indicated below

At pages 6-7, claims 2 and 3 have been rejected as being unpatentable over Kleinschmidt et al. in view of Pan et al., as applied to claim 1, and further in view of Martinez-Senac et al. and Barrow et al.

At page 8, claims 4 and 5 have been rejected as being unpatentable over Kleinschmidt et al. in view of Pan et al., as applied to claim 1, and further in view of Martinez-Senac et al. and Gursky et al.

At pages 8-9, claim 6 has been rejected as being unpatentable over Kleinschmidt et al. in view of Pan et al., as applied to claim 1, and further in view of Martinez-Senac et al. and Luhrs et al. and Vold et al.

At page 10, claims 7 and 8 have been rejected as being unpatentable over Kleinschmidt et al. in view of Pan et al., as applied to claim 1, and further in view of Martinez-Senac et al. and Vold et al.

At page 11, claim 9 has been rejected as being unpatentable over Kleinschmidt et al. in view of Pan et al., as applied to claim 1, and further in view of Martinez-Senac et al.

Applicants traverse these rejections.

In making these rejections of claims 2-9, the Examiner has relied the same primary reference, i.e., Kleinschmidt et al., and the same secondary reference, i.e., Pan et al., that were relied upon in the above discussed rejection under 35 U.S.C. §103(a) of claim 1. In rejecting claims 2-9, the Examiner has further included various sub-combinations of the supporting references in addition to Kleinschmidt and Pan. However, as indicated above with respect to the remarks presented regarding the obviousness rejection of claim 1, the contents of which are incorporated herein by reference in their entirety, Kleinschmidt et al. and Pan et al. do not render claim 1 obvious within the meaning of 35 U.S.C. §103(a). Each of the remaining claims, i.e., claims 2-9, depend from claim 1, and therefore are not rendered obvious by these further rejections.

In view of the forgoing, it is submitted that nothing in the cited references, whether taken alone or in combination, render the subject matter of claims 2-9 obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

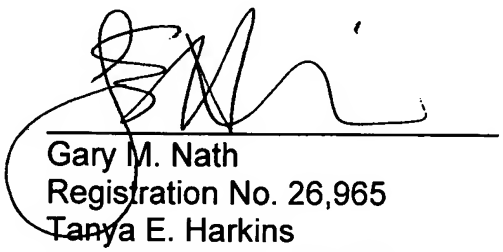
Conclusion

In view of the foregoing, Applicants submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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